

Amendments to the English Language Translation of the Specification:

Immediately before paragraph [0001] add the following new sub-headings and text:

-- CROSS-REFERENCE TO RELATED APPLICATIONS

This is a U.S. national stage of International Application No. PCT/EP2005/001984, filed on 25 February 2005. Priority is claimed on German Application No. 10 2004 009 934.0, filed on 26 February 2004.

BACKGROUND OF THE INVENTION

1. Field of the Invention --

Amend paragraph [0001] as follows:

[0001] The present invention concerns a method for analyzing a tissue sample ~~in accordance with the introductory clause of Claim 1~~ to determine its diseased tissue fraction while essentially preserving the genomic and/or proteomic and/or epigenomic and/or biophysical properties of the tissue sample.

Immediately before paragraph [0002], add the following new sub-heading:

-- 2. Description of the Related Art --

Immediately before paragraph [0014], add the following new sub-heading:

-- SUMMARY OF THE INVENTION --

Amend paragraph [0014] as follow:

[0014] ~~The~~ An objective of the present invention is to make available a diagnostically suitable method for analyzing a tissue sample for diseased tissue fractions and/or other relevant components and their relation to one another, in which individual samples are subjected to a histological and a nonmorphological analytical evaluation.

Amend paragraph [0015] as follows:

[0015] This objective is achieved ~~with the features of Claims 1 and 2~~ by a method of analyzing a patient tissue sample to determine its diseased tissue fraction while essentially preserving the genomic and/or proteomic and/or epigenomic and/or biophysical properties of the tissue sample. The method includes preparing sections from the tissue sample, subjecting at least one of the sections to a histological/cytological examination, and subjecting at least another one of the sections to a non-morphological analytical testing. In the histological/cytological examination, at least one of a quantitative fraction of diseased tissue or cells and another morphological aspect of the at least one of the sections is determined by an image processing system, and the determined at least one of a quantitative fraction of diseased tissue or cells and another morphological aspect is used as a reference quantity on which evaluation of a result of the non-morphological analytical testing is based. In a variant of the method, a sample is taken from the tissue sample. Then at least one portion of the sample is subjected to a histological/cytological examination, and at least another portion of the sample is subjected to a non-morphological analytical testing.

Amend paragraph [0019] as follows:

[0019] The quantitative determination of the fraction of diseased tissue or diseased cells can be made, for example, by first staining a section and then evaluating it by an image processing system, especially a computer-assisted image processing system. A system of this type usually ~~consists of~~ includes an optical system (e.g., microscope), an image acquisition system (e.g., CCD camera and image acquisition card), a computer, and suitable software. A large number of quantities can be quickly, automatically, and reproducibly determined from histological preparations with a system of this type.

Amend paragraph [0033] as follows:

[0033] Further sections of the series of sections, on the other hand, ~~consist of~~ include both nonmalignant tissue and tumor tissue and therefore, as described above, can be subjected, in accordance with the invention, to a histological/cytological examination, on the one hand, and to nonmorphological analytical testing, on the other hand. In this regard, it is especially promising to compare the histological/cytological and molecular-biological results that are obtained with those of the scrape preparation.

Amend paragraph [0039] as follows:

[0039] In ~~an especially~~ a preferred modification of the method of the invention, the sections or samples are prepared directly from the fresh tissue sample. This procedure guarantees that the genomic, proteomic, and/or epigenomic properties of the sample are preserved as well as possible. Sections can be prepared, for example, with a vibratome.

Amend paragraph [0040] as follows:

[0040] In another ~~especially~~ preferred modification of the method of the invention, the tissue sample is frozen before the sections or samples are prepared. This procedure also guarantees preservation of the genomic, proteomic, and/or epigenomic properties of the sample. The sections can be prepared, for example, with a microtome or cryotome.

Amend paragraph [0044] as follows:

[0044] ~~An especially~~ A preferred modification of the method of the invention is particularly well suited for use in clinical diagnostics. For clinical diagnostic purposes, a tissue sample that has been removed from the patient and is to be used for diagnosis is sent as quickly as possible to the pathology laboratory, where it is divided into two samples. The second sample is fixed and embedded for a thorough histological/cytological evaluation at a later time, while the first sample is immediately mounted on a slide, frozen, and cut in a microtome ("quick section"). Individual sections are then histologically stained and immediately evaluated by a pathologist, who reports his diagnosis to the treating physician. Particularly in intraoperative diagnosis, in which the operating surgeon, depending on the diagnosis reported to him by telephone by the pathologist, must make a decision about further surgical procedures that may be necessary, for example, the excision of axillary lymph nodes that may be additionally necessary after the removal of a breast carcinoma, this method has great importance, and, accordingly, great attention must be paid to optimization of the lapses of time.

Amend paragraph [0054] as follows:

[0054] Therefore, in ~~an especially~~ a preferred embodiment of the method of the invention, at least two sections are used for the histological/cytological examination. These sections are selected in a way that ensures that the section or sections sent for nonmorphological analytical testing were located between these sections in situ. In practice, two sections of a microtome section series that are not immediately adjacent to each other are stained and evaluated histologically/cytologically, while other sections of the microtome section series that are located between these sections are homogenized and subjected, for example, to an array-based mRNA analysis. The number of sections used for this purpose depends in this case, for example, on the amount of mRNA required for the analysis.

Amend paragraph [0069] as follows:

[0069] Furthermore, in other preferred embodiments, it is provided that the biomolecules to be detected are subjected to a labeling step and/or that the nucleic acids to be detected are subjected to an amplification step. The labeling step can ~~consist~~ include, for example, ~~in~~ circumscribing the mRNA molecules present in the divided sample into labeled cRNA molecules by the use of T7 RNA polymerase and Cy3-labeled ribonucleotides. Another example of a labeling step is the labeling of proteins present in the divided sample by the use of fluorescence-labeled antibodies or oligonucleotides. However, other labeling steps known from the present or future state of the art are also conceivable.

Amend paragraph [0070] as follows:

[0070] The amplification step can ~~consist~~ include, for example, ~~in~~ a PCR amplification technique, an RT-PCR amplification technique, or a different amplification technique in accordance with the present or future state of the art.

Amend paragraph [0072] as follows:

[0072] It is additionally provided that a method in accordance with any of the ~~preceding claims~~ methods described above can be used for developing a tumor data bank, for developing individualized cancer therapies, for adjustment of a ~~patient to an~~ patient's individualized cancer therapy, and/or for answering scientific questions.

Immediately before paragraph [0073], add the following new sub-heading:

-- **DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS** --

Amend paragraph [0075] as follows:

[0075] Sections of 6 μm thick are then prepared. The first and the fifth sections are mounted on a slide and stained with hematoxylin-eosin according to a standard protocol. The sections are first histologically evaluated. Both are identified as carcinoma of type X. The tissue composition is then quantitatively determined for each section by means of digital image processing. The results of the morphological analysis of the hematoxylin-eosin-stained preparations provide the following picture:

	Tumor Parenchyma	Tumor Stroma
Tumor A	80%	20%
Tumor B	50%	50%

Table 1. Histologically determined tissue composition of the two tumors.

On page 23, immediately before claim 1, add the following:

-- What is claimed is: --